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In Press, Journal Pre-proof What's this?

A natural compound melatonin enhances the effects of Nimotuzumab via inhibiting EGFR in glioblastoma

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Highlights

- This study exposes a complex relationship between circadian rhythms, melatonin, and brain tumors. It unfurls a deeper connection between circadian rhythm and brain tumors and proposes potential therapeutic significance for treating brain tumors. This offers potentially valuable insights for clinical diagnosis and treatment, thereby enhancing patients' quality of life. Besides improving patients' sleep and lifestyle management, the administration of a specific dosage of melatonin can inhibit tumor cell proliferation and growth. This approach might enhance the effect of existing treatments.
- This study provides an original proteomic analysis of gliomas after exposure to melatonin, revealing a proteomic panorama based on actual light control environments. Glioma is a major disease of the nervous system. With advancements in genomics, proteomics, and brain projects, treatment methods for glioma and other malignant tumors are rapidly evolving. The use of TMT11 quantitative proteomics technology enabled the identification and quantification of the entire proteome. This resulted in finding 748 significantly different proteins and discovering key markers for disease diagnosis, treatment, and prognosis. The mechanism of action and target of this small molecule drug has been detailed, paving the way for translational medicine to discover new treatments for gliomas.
- Utilizing protein-protein interaction data, we used AutoDock software to build an interaction model. A high-performance computing platform and global optimization algorithm were employed to construct a transmembrane structure model of the EGFR protein. Through 3D structural simulation and computer-aided drug design methods, we screened 20 structural analogs of melatonin

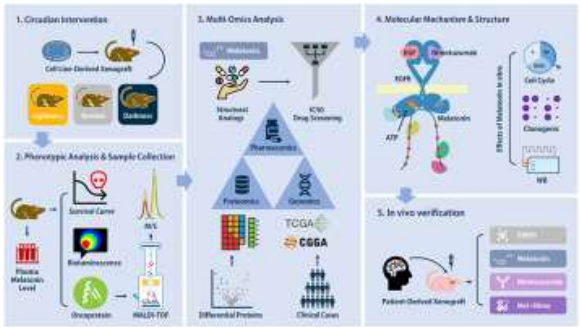
with high throughput. Our findings detailed the mechanism of action of melatonin in opposing the catalytically active pocket of EGFR tyrosine kinase. This groundbreaking discovery aids in understanding the functional mechanism of proteins associated with gliomas, guiding subsequent molecular biology verification experiments.

- The presentation of complex data in an accessible format is an important requirement, and advanced graphing methods can accurately depict research results in an engaging manner. This not only facilitates information transmission but also helps readers interpret results intuitively. By utilizing contour plotting, three-dimensional surface graphs, and sector shadow masks, we were able to make intricate multivariable connections both intuitive and clear. Simultaneously, well-crafted graphic summaries made the key principles and processes of the study evident at a glance. This greatly enriched readers' comprehension of the research content, potentially raising the readership and citation rate of the article.

Abstract

Sleep disorders are prevalent and debilitating symptoms in primary brain tumor patients, notably those receiving radiation therapy. Nevertheless, the relationship between sleep disorders, melatonin - a circadian rhythm regulatory hormone, and gliomas is underexplored. Melatonin exhibits various biological functions, one of them being anti-tumor activity. In the context of gliomas, often overexpressing EGFR, the humanized monoclonal antibody Nimotuzumab targets this marker. Our research discovered that variations in circadian rhythm significantly influence tumor growth in mice through impacting melatonin secretion. Harnessing proteogenomic, we identified that melatonin could inhibit the phosphorylation of EGFR and its downstream effectors, key elements in angiogenesis and tumor progression. Building on structural simulations, we propose that melatonin may amplify Nimotuzumab's anti-glioma efficacy by inhibiting EGFR TK dimerization. This proposition was validated in our in vitro and in vivo studies where melatonin synergistically augmented cytotoxicity and apoptosis in Nimotuzumab-treated glioma cells. Thus, melatonin shows promise as a beneficial addition to Nimotuzumab treatment in glioma patients.

Graphical abstract



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Introduction

Glioblastoma (GBM), a challenging-to-treat brain tumor, notably carries a bleak prognosis. Upon diagnosis, patients frequently encounter psychological distress, often manifesting as symptoms of insomnia [1], [2]. Other direct symptoms of these brain tumors, including headaches, nausea, and vomiting, can greatly impede an individual's ability to initiate and maintain sleep (3). In some cases, these brain tumors directly influence neural activity, thus disrupting usual sleep processes.

Circadian rhythms are innate 24-hour cycles of physiological, behavioral, and molecular activities. A cluster of cells in the hypothalamus known as the suprachiasmatic nucleus (SCN) his fundamental to maintaining these cycles. The SCN essentially functions as the brain's central timekeeper, managing peripheral clocks and the release of melatonin (4). Notably, melatonin, a vital hormone in regulating sleep-wake cycles, exerts various effects on cancer cells (5). These effects include inhibiting cell proliferation, promoting cell apoptosis, modulating the angiogenesis, and boosting immune responses [6], [7].

A significant body of research has started investigating the nexus between circadian rhythms, melatonin, and tumors, notably brain tumors. Brain tumors often induce sleep-wake disturbances and compromise the immune system [8], [9]. However, within the realm of glioma research, the underlying roles of insomnia and melatonin are still yet to be fully clarified: Does the disruption of circadian rhythms and melatonin metabolism tend to stimulate the development and progression of brain tumors? Alternatively, could it be possible that gliomas promote their own growth by influencing these circadian rhythms and melatonin levels? In terms of patient health outcomes, does melatonin impact the efficacy of treatments and subsequently affect the quality of life in glioma patients? Therefore, unearthing the innate connections and therapeutic implications of circadian rhythms and melatonin in managing brain tumors is a critical and promising field of study.

Recent studies have suggested that melatonin may have anti-tumor effects on glioma by modulating multiple signaling pathways (10). Cancer Cell growth inhibition appears not to be dependent on the activation of melatonin membrane receptors. Instead, it seems to be connected to a decrease in baseline intracellular free radical levels by 30%. The increase in the basal redox state of cells, and the constitutive activation of tyrosine kinase receptor pathways, including the ERK, AKT, and PKC signaling pathways, facilitate gliomas progression, leading to the constitutive activation of the redox-dependent survival transcription factor NF-κB [11], [12]. This suggests melatonin's ability to alter the cellular redox state might result in the inactivation of the RTK/PKC/AKT pathway. In this study, we aim to investigate the potential anti-tumor effects of melatonin on glioma by evaluating its role in inducing apoptosis, inhibiting proliferation, migration and invasion, modulating angiogenesis and impact on glioma stem cells, and enhancing the sensitivity of glioma cells to Nimotuzumab treatment. We also discuss the potential clinical applications of melatonin as an adjuvant therapy for glioma patients.

Section snippets

Chemical reagents

The Melatonin was purchased from Merck (444300-1GMCN, Darmstadt, Germany), the Nimotuzumab was purchased from Theramabs (TM-Nimo-02012018, Shanghai, China), the EGFR and EGF protein for kinase assay from Sigma (14-531-M/ GF316, MO, USA), the EGFRvIII protein for kinase assay from ACROBiosystems (EGI-H52H4, DE, USA),the molecular diagnostic grade ATP from Roche (04980824103, Basel, Switzerland), the ADP-GloTM kinase assay kit was purchased from Promega (V6930, WI, USA)….

Cell lines and cell culture

The human glioma (U118-MG, ...

Altering circadian rhythms affects both melatonin levels and survival in mice with glioma

In an endeavor to elucidate the correlation between circadian rhythms, melatonin levels, and glioma progression, we carried out informed experiments on mice with different light-dark cycles. These cycles are fundamental to regulating our biological clocks. The experiment was designed with three groups of mice experiencing distinct light-dark cycles (Fig.1A). The first group was exposed to unbroken light (5000K, 800lm, 0:00-24:00) for 24 hours, the second experienced an orthodox circadian rhythm ...

Discussion

The connection between melatonin, sleep disorders, and gliomas is multifaceted and intriguing. Gliomas and other brain tumors can disrupt the normal functioning of the brain, including the areas responsible for sleep regulation. This disruption, coupled with the stress and anxiety that often accompany a cancer diagnosis, can contribute to sleep disorders and insomnia in patients [22], [23]. Melatonin, as we know, plays a significant role in regulating sleep-wake cycles. In health, it is...

Declaration of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper....

Data and materials availability:

All data are available in the main text or the supplementary materials....

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